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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 27116-701.301

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on _____

Signature _____

Typed or printed name _____

Application Number	Filed
09/426,792	Oct. 22, 1999

First Named Inventor: Dennis T. Mangano

Art Unit	Examiner
1614	P. G. Spivack

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☒ attorney or agent of record.
Registration number 25,227.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

Albert P. Halluin
Signature

Albert P. Halluin
Typed or printed name

650/565-3585
Telephone number

January 27, 2006
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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ELECTRONICALLY FILED JAN. 27, 2006

PATENT
Attorney Docket No.: 27116-701.301

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Confirmation No. 2354
Applicant: Dennis T. Mangano	Group Art Unit: 1614
Serial No.: 09/426,792	Examiner: SPIVACK, P.G.
Filed: October 22, 1999	Customer No. 021971
Title: METHODS FOR REDUCING MORTALITY AND MORBIDITY BY POSTOPERATIVE ADMINISTRATION OF A PHARMACOLOGIC CARDIOVASCULAR AGENT	

Mail Stop AF
Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22314

PRE-APPEAL BRIEF CONFERENCE BRIEF

Introductory Comments/Interview Summary:

This brief is responsive to the second Final Office Action mailed November 7, 2005, and as such we have enclosed a Pre-Appeal Conference Brief and a Notice of Appeal for the above-referenced application. On September 22, 2005 a Notice of Appeal was filed and the $250 fee was paid. However, in the second Final Office Action mailed November 7, 2005 the examiner withdrew finality of the first Final Office dated June 23, 2005, so it is believed that no fee for an extension of time or for the second Notice of Appeal is due. Reconsideration is respectfully requested. Please reconsider the rejections of record in the above-referenced application as follows:

Summary of Claims

Claims 5, 7-14, 17-49 and 52 are cancelled. Claims 1-4, 6, 15, 16, 50, 51, 53, and 54 are currently pending and for the convenience of the Review Panel they are set forth in Attachment A.

REMARKS

This Pre-Appeal Brief is in response to the Examiner's Final Office Action mailed November 7, 2005. Even though new grounds rejections were made, the Examiner made this action final. Applicant submitted amended claims in view of the discussions with the Examiner during an interview at the USPTO.

This application has been pending via its prior filings since December 3, 1996.

The pending claims are drawn to methods comprising intravenous administration of a β_1-adrenergic blocking agent *immediately after surgery* and administration of the agent daily thereafter until symptoms of cardiovascular stress are reduced, wherein the β_1-adrenergic blocking agent is administered *near the maximum effective dose* of the agent. Applicant's invention is drawn, in part, to the surprising discovery that intravenous administration of a near maximum effective dose of a β_1-adrenergic selective blocker *immediately after surgery and daily thereafter* reduces cardiovascular complications. Dr. Dennis Mangano's declaration under Rule 132, previously filed on April 8, 2005, stated that, at the time of filing, he understood the phrase administration "immediately after surgery" to mean that administration occurs prior to a patient's emergence from anesthesia following surgery.[1]

Intravenous administration of maximum effective doses of a β_1-adrenergic blocker during the period prior to emergence from anesthesia offers significant advantages over the prior art, including the ability to administer the agent to the patient while he or she is still in an anesthetic state and thereby, unable to swallow the β_1-adrenergic blocker in oral form. Additionally, the claimed method involves administration of the agent during the anesthetic state immediately after surgery in which patients typically exhibit poor bioavailability.

This invention has had remarkable success in the clinic in terms of benefits to patients.

[1] Mangano Declaration of April 8, 2005, at paragraph 16.

Rejection Under 35 U.S.C. § 103(a)-Obviousness

Claims 1-6, 15, 16, and 50-54 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Matangi *et al.* (Can. J. Cardiol., 5(4): 229-234 (1989)).

First, Applicants note that claims 1-4, 6, 15, 16, 50, 51, 53, and 54 are currently pending.[2]

Applicant respectfully traverses the rejection as Matangi *et al.* does not teach or suggest the presently claimed methods. Specifically, Matangi *et al.* does not teach or suggest administration of a near **maximum effective dose** of a β_1-adrenergic blocking agent **immediately after surgery**. That is, Matangi *et al.* does not teach or suggest administering the β_1-adrenergic blocking agent in the time period **prior to a patient's emergence from anesthesia following surgery**.

Matangi *et al.* does not teach or suggest intravenous administration of a β_1-adrenergic blocking agent in an amount near the maximum effective dose in the time period immediately after surgery, as is recited in the claims. Instead, Matangi *et al.* discloses intravenous administration of 5 mg atenolol within 3 hours of the completion of surgery, followed by a second intravenous dose 24 hours later, and subsequent oral administration of 50 mg atenolol for six days.[3] *See* Matangi *et al.*, abstract. Dependent claim 51 recites that the maximum effective dose of atenolol for intravenous administration is about 10 mg every 12 hours. Therefore, the dose of atenolol taught in Matangi *et al.* is less than the average maximum effective dose proscribed for atenolol.

In addition, Applicant respectfully disagrees with the Examiner's erroneous contention that the time period "within 3 h of the completion of surgery" disclosed in Matangi *et al.* encompasses the time period "immediately after surgery" recited in the claims. The phrase administration "immediately after surgery" refers to administration prior to a patient's emergence from anesthesia following surgery. In contrast to the claimed methods, Matangi *et al.* discloses intravenous administration of only 5 mg atenolol within 3 hours of the completion of surgery, followed by a second intravenous dose 24 hours later. Firstly, 5 mg is not a normal maximum dose of atenolol,

[2] The Summary Sheet for the Office Action incorrectly states that claims 1-16 and 50-54 are pending.

[3] The Examiner incorrectly stated that Matangi *et al.* teaches "[a]tenolol therapy was thereafter continued daily for eight days." *See* Office Action at page 2, last paragraph (emphasis added).

and 24 hours later is too late for the desired affect as herein claimed. Because Matangi *et al.* does not teach or suggest administering a β_1-adrenergic blocking agent before the patient emerges from anesthesia following surgery, Matangi *et al.* does not teach or suggest the claim limitation of "immediately after surgery."

Moreover, the Examiner's unsupported assertion that "[a] dose higher than 100 mg is unlikely to produce any further benefit"[4] and "[a] dosage of 100 mg/day orally or 10 mg bid intravenously is conventional"[5] is inappropriate. According to MPEP 2144.02, "when an examiner relies on a scientific theory, **evidentiary support for the existence and meaning of that theory must be provided**."[6] Here, the Examiner fails to provide any reference or scientific reasoning to support the allegation that doses of a β_1-adrenergic blocking agent exceeding 100 mg do not provide benefit to a patient, or that an oral dose of 100 mg/day of a β_1-adrenergic blocking agent or an intravenous dose of 10 mg bid of a β_1-adrenergic blocking agent is "conventional."

Lastly, the Examiner asserts that the patient risk factors recited in dependent claim 50 are disclosed in Matangi *et al.* at Table 2 on page 230. Claim 50 depends on claim 1 and recites that the patient has had previous vascular surgery or has at least two of the following cardiac risk factors: older than 65 years, hypertensive, current smoker, serum cholesterol level of at least about 6.2 mmol/L, or diabetes mellitus. According to column 1 on page 230 of Matangi *et al.*, patients *excluded* from the study included those "aged over 70 years; second or subsequent coronary artery bypass graft operation... [and] brittle type 1 diabetes mellitus." Thus, the patient risk factors recited in claim 50 are not disclosed in Matangi *et al.*

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[4] *See* Office Action at page 3, first paragraph.
[5] *See id.*
[6] *See* MPEP 2144.02 citing *In re Grose*, 592 F.2d 1161 (CCPA 1979).

Applicant respectfully asserts that the present claims are non-obvious over Matangi *et al.* because the cited reference does not teach or suggest intravenous administration of **a near maximum effective dose** of β_1-adrenergic blocking agent **immediately after surgery** and daily thereafter, as is recited in the present claims.

Accordingly, Applicants respectfully request that the above rejection of claims 1-6, 15, 16, and 50-54 be withdrawn.

CONCLUSION

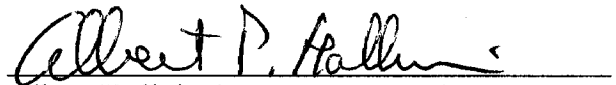
Applicants respectfully solicit the panel of Examiners to grant a finding of allowance on the existing claims and expedite issuance of this patent application. Should the panel have any questions, the panel is encouraged to telephone the undersigned.

The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to Deposit Account No. 23-2415 (Attorney Docket No. 27116-701.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Date: January 27, 2006

By: 

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Attachment A

1. (Previously presented) A method for reducing cardiovascular disease complications in a patient following surgery comprising the sequential steps of:

(i) intravenously administering to the patient a β_1-adrenergic blocking agent immediately after surgery; and thereafter

(ii) administering the agent daily thereafter until symptoms of cardiovascular stress are reduced,

wherein the agent is administered near the maximum effective dose of the agent while the patient's heart rate is greater than or equal to 65 bpm, the patient's systolic blood pressure is greater than or equal to 100 mm Hg, and the patient evidences no congestive heart failure, third degree heart block, or bronchospasm.

2. (Previously presented) The method of Claim 1 in which the agent is administered in step (ii) daily in the period after surgery until hospital discharge.

3. (Previously presented) The method of Claim 2 in which the agent is administered in step (ii) daily in the period after surgery for at least three days.

4. (Previously presented) The method of Claim 2 in which the agent is administered in step (ii) daily in the period after surgery for up to seven days.

5. (Cancelled)

6. (Previously presented) The method of Claim 1 in which the β_1-adrenergic blocking agent is atenolol.

7. - 14. (Cancelled)

15. (Original) The method of Claim 1 in which the patient suffers from coronary artery disease.

16. (Original) The method of Claim 1 wherein the patient is at risk for coronary artery disease.

17.-49. (Cancelled)

50. (Previously presented) The method of Claim 1 in which the patient has had previous vascular surgery or has at least two of the following cardiac risk factors: older than 65 years, hypertensive, current smoker, serum cholesterol level of at least 6.2 mmol/L, or diabetes mellitus.

51. (Previously presented) The method of Claim 1 in which the agent is atenolol and the maximum effective dose is about 100 mg/day orally or about 10 mg BID intravenously.

52. (Cancelled)

53. (Previously presented) The method of Claim 1 wherein the agent is administered in step (ii) daily for six months following surgery.

54. (Previously presented) The method of Claim 1 wherein the agent is administered in step (ii) daily for eight months following surgery.